SPECIAL ISSUE ARTICLE

Common Neonatal Skin Lesions: Melanocytic Nevi, Pigment Alterations, and Nonmelanocytic Nevi

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ABSTRACT

Birthmarks are common in the healthy population and are generally harmless. Certain presentations, however, raise concern for associated syndromes or potential complications. It is important for pediatricians to be familiar with both harmless and potentially concerning birthmarks. This article discusses congenital melanocytic nevi, café-au-lait macules, hypomelanotic macules, nevus depigmentosus, nevus anemicus, epidermal nevi, and nevus sebaceous, including potential syndromes and complications. **[*Pediatr Ann*. 2019;48(1):e23-e29.]**

Although birthmarks are common in the healthy population, it is important for pediatricians to be able to distinguish harmless birthmarks from rarer ones that should prompt further investigation. The term "birthmark" implies that these lesions are all present at birth. However, some birthmarks may appear only after the first months or even years later. These "delayed" birthmarks are hypothesized to develop in-utero and, therefore, are still categorized with other congenital anomalies, even though they present later in life.

Melanocytic nevi (congenital melanocytic nevi [CMN]), pigment alterations (café-au-lait [CAL] macules, hypomelanotic macules, nevus depigmentosus [ND], nevus anemicus—the latter a vascular malformation rather than a true pigment alteration), and nonmelanocytic nevi (epidermal nevus [EN], nevus sebaceous [NS]) are discussed below. The term nevus refers not only to melanocytic overgrowths, but also more broadly to any hamartoma, including growths derived from various epidermal and dermal components. Although the lesions discussed are common in the healthy population, they may be associated with syndromes or underlying systemic anomalies and are important for pediatricians to recognize to facilitate testing and early diagnosis.

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CONGENITAL MELANOCYTIC NEVI

CMN are pigmented lesions that present in 1% of the population at birth or rarely within the first 2 years of life.[1] They likely arise due to aberrant proliferation and migration of melanocytes during embryogenesis. This phenomenon is thought to lead to a focal increase in melanocyte density and proliferative capacity within the dermis and along adnexal structures, including skin appendages such as hair follicles. CMN have different (albeit overlapping) clinical, dermatoscopic, and histologic features compared with common acquired melanocytic nevi ("moles"), and thus they are considered a distinct entity. Acquired nevi arise later in childhood and adulthood and are more clearly linked to genetic inheritance and also to sun exposure. CMN are an important entity to recognize given their potential association with complications, including developmental anomalies, neurocutaneous melanocytosis, melanoma, and psychosocial impairment.[2]

Clinical Features

CMN are red or brown, flat or minimally raised lesions at birth. They are most commonly classified based on projected size in adulthood: small (<1.5 cm in largest diameter), medium (1.5-19.9 cm), and large or giant (≥20 cm) (**Figure 1**). There are various tools to predict adulthood CMN size.[3,4] Based on one formula, CMN that are 12 cm on the head; 7 cm on the hands, feet, torso, forearms, arms, or buttocks; 5.8 cm on the thighs; and 6 cm on the legs otherwise at birth are considered large/giant.[4] Satellite lesions refer to smaller CMNs in the vicinity of a larger CMN and can present at birth or later in infancy and in childhood. Throughout childhood, CMN may become lighter or darker, may become thicker, and can develop surface rugosity, nodularity, color heterogeneity, and overlying coarse, thick, and long hair[5] (**Figure 2**). These qualities can lead to nevi that are cosmetically troublesome to patients, even when small.

Complications/Associations

Solitary small and medium CMN have a low risk of serious complications. Parents can be reassured that melanoma is unlikely and that clinical monitoring by their pediatrician is usually adequate. When two or more CMN or large/giant CMN are present, the risk of complications increases and evaluation by dermatology is essential.

One complication of large/giant CMN is neurocutaneous melanosis (NCM). NCM describes the presence of aberrant melanocytic proliferations within neural tissue, including the leptomeninges, brain parenchyma, and spinal cord. In one of the largest studies to date,[3] 2.6% to 17.4% of patients with large/giant CMN had symptomatic NCM (data in this study were derived retrospectively from the New York University Large CMN Registry and from a review of the literature, respectively). The study also supported the notion that posterior axial location (ie, back/buttocks) and numerous satellite lesions are risk factors for symptomatic NCM.[3] It is unclear exactly what percentage of all patients with NCM develop symptoms, but studies range from 2% to 72%,[6] with this wide variability ascribed to differences in criteria for magnetic resonance imaging screening (eg, not all patients with CMN were screened, likely with a bias toward higher-risk and symptomatic patients), and age at imaging. Symptoms include developmental delay, hydrocephalus, cranial nerve palsies, and seizures, and when present they portend a poor prognosis.[7] Symptoms typically arise within the first 3 years of life, with a second peak in the second and third decades of life. Traditional risk factors for NCM include increased number of satellite lesions (likely an independent risk factor), large/giant size, and involvement of the back.[8] More recently, some experts have proposed that the highest risk of NCM occurs with two or more CMN of any size or location.[9] Testing typically consists of a baseline MRI of the brain and spinal cord prior to age 6 to 8 months, before myelination is complete and obscures thorough evaluation, with subsequent reimaging based on symptoms. Pediatricians can play an essential role in facilitating this testing by early recognition of CMNs. Pediatricians should monitor for signs of central nervous system involvement and refer to neurology accordingly. Treatment is generally palliative, not curative, although small molecule inhibitors may play a role in the future

Regarding melanoma, patients with CMN are at increased risk, although the exact lifetime risk is not currently known, as different sources cite widely differing risk. With medium or small CMN, the risk is low, likely less than 1%.[10] If melanoma arises, it is typically around puberty or in adulthood.[2] Melanoma risk, especially in children, is greatest in large/giant CMN and approximately one-half of cases in large/giant CMN arise in the first 5 years of life. Reports of overall lifetime risk range from 5% to 40%, although more recent data suggest the actual risk is closer to 5% or less.[2,4,10] Melanoma usually arises deep within CMN and requires careful visual and tactile inspection to find deep nodules and masses.

Perhaps one of the most difficult aspects of managing CMN is distinguishing benign secondary growths, termed proliferative nodules, from melanoma. Pediatricians should assess for new nodules or bleeding arising from CMN and for *de novo* skin lesions and refer to dermatology accordingly. Pediatricians can also facilitate compliance with sun protection and remind patients of dermatologic screening appointments, the interval of which is individualized to each patient and dermatologist.

CAFÉ-AU-LAIT MACULES

Café-au-lait macules or spots (CAL) are well-defined flat brown macules or patches. They may be present at birth but more commonly arise during infancy and early childhood. One-quarter to one-third of healthy children may have one or more CAL.[11,12] They are more common in people with darker skin, as well as a subset of people with fair complexions.[11,12] Multiple CAL may be a normal feature, but children with three or more CAL should be evaluated by a pediatric dermatologist or geneticist to rule out a genetic disorder such as neurofibromatosis type 1 (NF1) or Noonan syndrome, as having three or more CAL is not common in the general, healthy population. As with other pediatric conditions, genetic syndromes present dynamically over time; therefore, the number of CAL needs to be evaluated in the context of the child's age and other clinical features.

Clinical Features

CAL are named for their "coffee with milk" light brown color on fairer skin and appear darker than the patient's background skin regardless of ethnic background. The borders can be smooth or jagged, and the shape is often ovoid. They are asymptomatic, remain flat throughout life, can be located on any cutaneous surface, and range in size from a few millimeters to 20 cm or more.

Complications/Associations

The presence of six or more CAL larger than 5 mm in diameter in prepubertal children or larger than 15 mm in postpubertal youth should prompt consideration for NF1 and fulfills 1 of 2 clinical criteria required for diagnosis.[13] NF1, a neurocutaneous disorder caused by mutations in the neurofibromin 1 tumor suppressor gene, is associated with macrocephaly, neurologic and behavioral impairment, and increased risk of certain malignancies. Other diagnostic features of NF1 arise later in infancy and childhood, with the exception of plexiform neurofibromas (PNs), which are congenital but may not become evident until childhood, depending on their size and location. Historically, PNs were thought to be present in 25% of NF1 patients, but more recent data with MRI screening suggests that number is greater than 50%.[14] They classically present as sagging soft tumors with a "bag of worms" texture or slightly raised hyperpigmented plaques that may resemble large CMN. PNs often have an infiltrative pattern of growth, may be disfiguring, and can lead to functional impairment. They carry a 2% to 11% lifetime risk of transformation into malignant peripheral nerve sheath tumors.[14]

All children with NF1 should be evaluated in a neurofibromatosis center or by a NF1 expert as they require lifelong age-appropriate screening, including screening for optic gliomas, hypertension, learning disabilities, attention-deficit/hyperactivity disorder, scoliosis, and malignancy. The decision whether to perform genetic testing to confirm NF1 in the setting of a clinical diagnosis is controversial and should be made by NF1 experts.[15,16] Less common syndromes associated with multiple CAL include Legius (neurofibromatosis-like) syndrome, which has no systemic involvement, and Noonan syndrome.[17]

McCune-Albright syndrome (MAS) is the other major concern related to CAL. The presence of a large CAL, typically with sharp midline demarcation and jagged, irregular borders resembling the "coast of Maine" raises concern for MAS (**Figure 3**). It is caused by activating mutations in the *GNAS* gene, which encodes the stimulating alpha subunit of the guanine nucleotide-binding protein (G protein) complex, which is involved in molecular signal transduction. MAS is associated with skeletal abnormalities and endocrine disorders. Bony abnormalities are due to polyostotic fibrous dysplasia, which can lead to bone pain, pathologic fractures, skeletal and gait abnormalities, and facial asymmetry. Endocrine abnormalities include precocious puberty in 85% of females (it also occurs in males), hyperthyroidism in about 33% of patients, acromegaly, phosphate wasting, and rarely neonatal Cushing syndrome, which is potentially fatal.[18] The presence of a segmental CAL warrants clinical monitoring for these issues and referral to orthopedics, endocrinology, and genetics as needed.

Figure 1. Solitary medium congenital melanocytic nevi (CMN) on the chest of a child. Note the surface rugosity, presence of darker foci within the CMN, and fading at the periphery, all of which are normal features. This CMN is low risk for neurocutaneous melanosis and melanoma. (Used with permission from Dr. Bernard Cohen, Johns Hopkins University.)

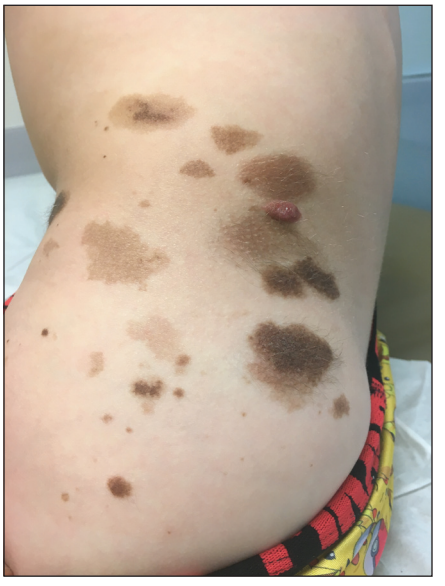

Figure 2. Multiple healthy-appearing small and medium congenital melanocytic nevi varying in color from pink to tan to light brown to dark brown. (Used with permission from Dr. Bernard Cohen, Johns Hopkins University.)

HYPOPIGMENTED BIRTHMARKS: NEVUS DEPIGMENTOSUS AND HYPOMELANOTIC MACULES

ND and hypomelanotic macules (HM) are white, minimally pigmented flat spots that occur due to decreased production of melanin and impaired transfer of melanin to keratinocytes. ND tend to be few in number and do not have well-established systemic implications,

Figure 3. Segmental café-au-lait patch on right upper back with jagged, well-defined borders.

whereas HM can be few to many in number, may have characteristic shapes, and can be a marker of tuberous sclerosis complex (TSC). The distinction between the two lesions is not always obvious.

Clinical Features

HM and ND are present at birth, although they may not be immediately apparent given the lighter color of newborn skin, and can be more difficult to appreciate in lighter-skinned people until tanning occurs. The overlying hair may be white, sometimes leading to a circumscribed white patch of hair on the scalp termed poliosis.

The presence of one or two HM has been described in 4.7% of healthy patients and does not typically raise concern for a syndrome.[19] On the other hand, the presence of three or more HM, especially if lancet-shaped, raises concern as this is one major criterion for TSC. "Confetti-like" HM describes the pattern of hundreds of small (1-2 mm) white macules most commonly on the extremities, especially the shins. Lancet or "ash leaf" HM are rounded at one end and tapered at the other (resembling the leaf of the ash mountain tree) and are common on the trunk. Both confetti-like and ash leaf HM are characteristic of TSC but are less common than small polygonal or thumbprint-shaped lesions. HM are best visualized with a Wood's lamp. HM are the first cutaneous lesion in TSC with numerous other skin findings developing over time.

Complications/Associations

Much like CAL, HM themselves are benign but serve as a marker for a potential genetic syndrome. Similarly, HM may be the first manifestation of TSC and appear before the classic triad of seizures, mental retardation, and facial angiofibromas termed adenoma sebaceum. A history of seizures would further raise suspicion for TSC and warrant further evaluation. Some experts recommend initial testing with an echocardiogram to assess for cardiac rhabdomyomas, which are common in neonates and infants with TSC but regress with time, and MRI of the brain to assess for cortical tubers, which are present in 80% of children younger than age 2 years.[20] Of note, pigmentary mosaicism is a separate entity with extensive blaschkoid hyper- or hypopigmentation without textural changes, elevations, or depressions but can be associated with multisystem manifestations **(Figure 4)**.

NEVUS ANEMICUS

Nevus anemicus (NA) is a congenital vascular anomaly found in 1% to 5% of the general population that also appears as a white patch somewhat similar to a ND.[21,22] The etiology, however, is different because the white color of NA is attributed to increased sensitivity to catecholamines in the local vasculature, leading to constitutional vasoconstriction.

Clinical Features

NA remains flat and smooth throughout life and has irregular but well-defined borders resembling paint splatter on a canvas. It is most commonly located on the trunk, especially the chest, but can also be found on the extremities, head, and neck. The borders of NA can be accentuated by lightly rubbing the area to cause vasodilation. The surrounding normal skin will become red while the NA will retain its white, vasoconstricted color (**Figure 5**). Conversely, the normal skin at the edge of a NA may be blanched using a glass slide, which will cause the NA to "disappear" as the normal skin is vasoconstricted. In contrast to a NA, a ND should become pink or red when rubbed or with temperature alterations and will not disappear completely with blanching, as the vasculature is normal.

Complications/Associations

NA generally represents an isolated finding, although recent literature suggests an association with NF1, which is of particular significance given its presence earlier in life compared with most of the current NF1 diagnostic criteria.[21,22] Recent studies show that the prevalence of NA in patients with NF1 is higher compared to the general population, including 51% of NF1 patients compared with 2% of age-matched controls in one study[21] and 28% of NF1 patients in another.[22] The inclusion of NA in the diagnostic criteria for NF1 has, therefore, been proposed.

EPIDERMAL NEVUS AND NEVUS SEBACEOUS

EN and NS represent hamartomatous overgrowth of normal skin components due to somatic mutations acquired in-utero postfertilization. As embryonic precursor cells divide, *de novo* mutations may occur and are transmitted

to daughter cells. A mutation early in development will lead to more numerous, extensive, and sometimes bilateral lesions, because more daughter cells will carry the mutation. Multiple organ systems can be affected if the mutation occurs in a pluripotent progenitor cell. The lines of Blaschko refer to the roadmap of embryonic keratinocyte migration and are curvilinear and whorled in shape and demarcated at the midline.[23] Skin lesions appearing in this pattern are referred to as "blaschkolinear."

EN represent overgrowth of epidermal components and are a classic example of blaschkolinear lesions (**Figure 6**). NS represent overgrowth of dermal mesenchymal elements including sebaceous and apocrine glands, and they lack normally developed hair follicles. Despite being composed of dermal elements, NS may also follow the lines of Blaskcho. This distribution is attributed to the role of keratinocytes in inducing differentiation and growth of underlying mesenchymal elements (including sweat glands and hair follicles) during development. Some hamartomas have overlapping histologic features of both EN and NS, which may resemble each other clinically and have similar associated potential complications and are, therefore, discussed together.

Clinical Presentation

EN and NS typically appear flat or minimally raised at birth. As with other birthmarks, they may appear later in infancy or rarely in adulthood. EN tend to occur on the trunk and extremities in a blaschkolinear shape, whereas NS tend to occur on the scalp and face and may be ovoid or linear with overlying alopecia (**Figure 7**). Both types of nevi may be pink, skin colored, or light to dark brown in color. NS typically acquire a yellow hue and become more "bubbly" appearing and raised nearing puberty as the sebaceous and apocrine gland components mature under the influence of androgens.[24] This often progresses to a more "warty" look.

Figure 4. Hypopigmentation along lines of Blaskcho on the back representing pigmentary mosaicism.

Figure 6. Epidermal nevus on the posterior neck presenting as tan to brown discontinuous plaque in blaskcholinear distribution.

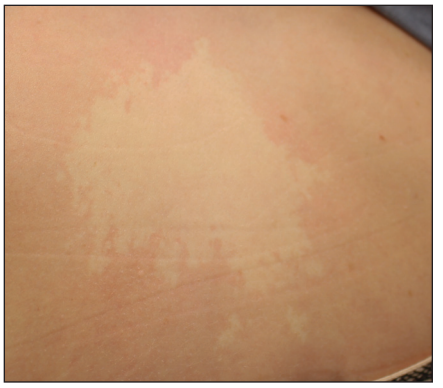

Figure 5. Nevus anemicus with blanched-appearing white color.

Figure 7. Nevus sebaceous presenting as alopecic tan-yellow plaque on the scalp.

Nevus comedonicus (NC) is a unique entity comprised of grouped follicular openings that resemble open comedones (eg, "blackheads"). Inflammatory papules, cystic nodules, and acne-like scarring may arise during puberty. Various mutated genes have been identified in NS including fibroblast growth factor receptor 2 (*FGFR2*). Germline mutations in *FGFR2* lead to Apert syndrome, which is characterized by severe, early-onset, widespread cystic acne and skeletal abnormalities in-

cluding synostosis (abnormal fusion) of the cranium, vertebral bodies, and bones of the hands and feet. NC syndrome can present with similar systemic findings when the mutation occurs early in development.[25]

Complications/Associations

Benign and malignant neoplasms occur in 10% to 20% of NS[24] and less commonly in EN, typically after puberty but occasionally in childhood. Basal cell carcinoma is the most common malignancy arising within them. The risk of this slow growing, locally proliferative carcinoma is believed to be as high as 0.8% in NS,[26] far lower than described in early reports. The risk is quite discrepant in the literature due to misdiagnosis of more common benign growths that can appear similar to basal cell carcinoma on histology. Aggressive skin cancers are rare but have been reported.

Traditionally, NS were excised prophylactically. However, there is no consensus regarding the true benefit of doing this nor best timing of prophylactic surgical excision, and therefore patients should be referred early in life to dermatology for further discussion and management. Cosmesis is often a concern as the lesions become more raised and textured through childhood and adolescence, especially during puberty. Deferring surgery until adolescence allows selection for more cosmetically concerning nevi and facilitates removal under local anesthesia. Laser ablation is another treatment option.

Extensive EN and NS raise concern for associated syndromes that most commonly involve the musculoskeletal, neurological, ocular, cardiac, and urologic systems. These syndromes have been described by numerous names in the literature, including linear epidermal nevus syndrome (LENS) and linear nevus sebaceous syndrome (LNSS). Regardless of terminology, most important is the concept that these syndromes likely occur due to early mutations in progenitor cells that affect multiple tissue types. The syndromes are often characterized by seizures beginning in the first year of life and impaired intelligence. Other anomalies are quite varied and are described in detail elsewhere.[27] Patients with suspected LENS or LNSS should be referred for evaluation by dermatology, at a minimum, as well as neurology, ophthalmology, and cardiology based on clinical signs and symptoms. Patients should also be monitored for hypophosphatemic rickets.

CONCLUSION

The birthmarks described above are quite common, important to recognize, and at times difficult to distinguish from one another. Clinicians can hone their diagnostic skills by making note of these generally benign findings during routine physical examination. Pediatricians can play a crucial role in reassuring the family or facilitating the early diagnosis of syndromes associated with these birthmarks.

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